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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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GROUP 1600

Application Number: 09/909,574
Filing Date: July 20, 2001
Appellant(s): SKRALY ET AL.

Patrea Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 22, 2007 appealing from the Office action mailed March 22, 2007.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skraly et al. *(Polyhydroxyalkanoates Produced by Recombinant E. coli*, Poster at Engineering Foundation Conference: Metabolic Engineering, 1998, "Skraly"), Madison et al. (*Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic.* Microbiol Mol Biol Rev. 1999 Mar;63(1):21-53, "Madison"), and BRENDA database ("EC 1.1.1.202"– ("BRENDA"). Claims 1-4 and 6-10 are drawn to a method of producing PHAs by providing an *E. coli*, which expresses acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase, wherein said bacteria is genetically engineered to express polynucleotides that encode a diol oxidoreductase or aldehyde dehydrogenase, wherein the enzyme expressed by the bacteria convert 1,6-hexandediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol into 6-hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate or 2-hydroxypropionate monomers, respectively, and producing PHAs having a weigh-average molecular weight of at least 300,000 Da.

Skraly discloses a method of producing PHA from 1,3-propanediol using recombinant *E. coli* expressing PHA synthase and diol oxidoreductase (pages 8-9),

wherein said diol is oxidized to its corresponding aldehyde and then converted to its corresponding hydroxyalkanoate monomer via an aldehyde dehydrogenase and CoA transferase (page 8). *E. coli* produces aldehyde dehydrogenase naturally. Skraly also discloses (1) PHA monomers other than 3-hydroxybutyrate that can improve flexibility and reduce crystalline of the resulting PHA polymer, such as 5-hydroxyvalerate and 4-hydroxybutyrate (page 6) and (2) new inexpensive starting materials for PHA synthesis, such as diols, 1,3-propanediol, 1,5-pentanediol, 1,4-butanediol and 1,2-propanediol, which are converted into their respective PHA monomers, 3-hydroxybutyrate, 5-hyroxyvalerate, 4-hydroxybutyrate and 2-hydroxypropionate (pages 1, 6 and page 8).

The difference between the reference of Skraly and the instant invention is that the reference of Skraly teaches does not teach a method of producing PHA from 1,6-hexanediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethandiol and 1,2-propanediol using an *E. coli* expressing diol oxidoreductase and acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase.

Madison is cited here to provide evidence to support the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. Madison ealso teaches that the molecular mass of PHAs produced varies from 50,000 to 1,000,000 Da and bacterially produced PHAs have a high molecular mass (page 22). As applicants have stated, "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and

integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief filed June 5, 2006, pages 24-25).

BRENDA discloses several diol reductases that oxidize diols and that have been cloned and expressed in *E. coli,* including the *K. pneumoniae* diol oxidoreductase used by Skraly and in the instant invention. Further, BRENDA discloses a 1,3-propanediol dehydrogenase isolated from C. *freundii* which oxidizes several diols, 1,3-propanediol, 1,2-propanediol and 1,4-butanediol, and its expression in *E. coli* (pages 2-3). This enzyme has been cloned and expressed in *E. coli* (pages 10 and 12) as evidenced by Daniel et al. (J Bacteriol. 1995 Apr;177(8):2151-6, "Daniel"). Daniel also teaches that said enzyme oxidizes all primary, secondary and tertiary alcohols (Daniel on page 5152). Even though 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol are not explicitly listed as one of the substrates, since the enzyme is able to oxidize primary alcohols and diols containing two primary alcohols, one having ordinary skill in the art would have reasonably expect the enzymes to oxidize 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol. Also, one having ordinary skill in the art would have used other diol reductases of BRENDA to oxidize the recited diols.

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art to use the method of Skraly et al. in making PHAs by using other diols, such as 1,6-hexandediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol, by converting said diols into their respective PHA monomers using a recombinant *E. coli* that expresses acyl-CoA

transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase as taught by Madison and that also expresses a diol oxidoreductase. One of ordinary skill in the art would have been motivated to produce PHA from the recited diols in order to produce novel PHAs using inexpensive starting materials. One of ordinary skill in the art would have had a reasonable expectation of success since Skraly teaches a method of producing PHAs from a diol using a diol oxidoreductase/aldehyde dehydrogenase, Madison teaches expression of genes necessary for PHA synthesis and BRENDA teaches several diol oxidoreductases that have been cloned into *E. coli* that have a wide range in substrate specificity. One having ordinary skill in the art would have had a reasonable expectation of success since production of PHAs in recombinant organism, such as *E. coli*, expressing enzymes necessary for PHA production is well known in the art and diol oxidoreductases, which have been cloned and expressed in *E. coli*, having a wide range of substrate specificity are well known in the art.

Therefore, claims 1-4 and 6-10, drawn to the methods as described above would have been obvious to one of ordinary skill in the art.

(10) Response to Argument

Beginning at the middle of p. 6 of the Brief, appellant summarizes case law relevant to obviousness under 35 U.S.C. 103(a).

Beginning at the middle of p. 9 of the Brief, appellant argues that while production of PHAs in genetically engineered bacteria and plants by engineering of such organisms with β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase using known pathyways was known in the prior art, appellant argues that the instant invention is drawn to production of PHAs in genetically engineered organisms using alternative pathways, providing cheap diols to form PHAs, and one skilled in the art would not have known what enzymes must be expressed by the engineered organism.

Appellant's argument is not found persuasive. Appellant argues that one skilled in the art would not have known what enzymes must be expressed by the engineered organism, yet points out that that "it was routine to identify enzymes having the appropriate specificity for the cheap substrates which would in turn yield the required monomers" (bottom of p. 9 to top of p. 10 of the Brief). Also, since Skraly discloses using an *E. coli* genetically engineered to express a 1,3-propanediol oxidoreductase isolated from *K. pneumoniae* and an aldehyde dehydrogenase (endogenous to *E. coli*) to convert a 1,3-propanediol oxidoreductase to its required PHA monomer, it would have been obvious to one having ordinary skill in the art to either use a 1,3-propanediol oxidoreductase isolated from *K. pneumoniae* or substitute other well known diol oxidoreductases, such as those disclosed by BRENDA, to achieve the predictable result of converting diols into their required PHA monomers.

Beginning at p. 10 through middle of p. 11 of the Brief, Appellant argues **(1)** that while Skraly discloses production of co-monomer P3HB-co3HV from 1,2-propanediol,

Skraly does not disclose a system that can covert diols (cheap substrates) into hydroxyalkanoate monomers, wherein the diols are selected from the group consisting of 4-hydroxybutyrate, 2-hyroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate; **(2)** that the examiner points to page 6 to show that Skraly discloses using 5-hydroxyvalerate and 4-hydroxybutyrate as monomers for producing PHAs, but the issue is not using 5-hydroxyvalerate and 4-hydroxybutyrate as monomers for producing PHAs, but whether or not the prior art teaches the selection of the enzymes to engineer the organisms to utilize cheap diol substrates to produce monomers; and **(3)** examiner has concluded that one could read into the disclosure that other diols could be utilized without providing any evidence that can be found in Skraly.

Appellant's arguments are not found persuasive. The rejection is not based on Skraly alone. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Skraly is relied upon for its teaching of a method of producing PHAs from a cheap diol by genetically engineering an organism expressing a 1,3-propanediol oxidoreductase and aldehyde dehydrogenase. The reference of BRENDA is relied upon for its disclosure of enzymes well known in the art that convert many different diols into their respective PHA monomers. Further, appellant points out "it was routine to identify enzymes having the appropriate specificity for the cheap substrates which would in turn yield the required monomers (bottom of p. 9 to top of p.

10 of the Brief). Therefore, it would have been obvious to one having ordinary skill in the art to generate PHAs comprising of 5-hydroxyvalerate, 4-hydroxybutyrate or 2-hydroxypropionate from 1,5-pentanediol, 1,4-butanediol or 1,2-propanediol, respectively, or convert other structurally similar diols, such as 1,6-hexanediol into 6-hydroxyhexanoate and 1,2-ethanediol into 2-hydroxyethanoate by using *E. coli* expressing diol oxidoreductase available in the art.

Further, examiner respectfully disagrees with appellant's analysis of the disclosure of Skraly.

(1) Skraly does disclose alternative pathways for producing PHAs from the diols recited in the claims, such as 1,2-propanediol (converted to 2-hydroxypropionate), 1,4-butanediol (converted to 4-hydroxybutyrate) and 1,5-butanediol (converted to 5-hydroxyvalerate) (pages 1, 6-7 and 9) and a method of engineering an organism to produce PHAs from two different diols using an E.coli genetically engineered to express 1,3-propanediol oxidoreductase and an aldehyde dehydrogenase (endogenous to *E. coli*)(see p.8).

(2) Page 6 of Skraly does not merely disclose use of 5-hydroxyvalerate and 4-hydroxybutyrate as PHA monomers, but Skraly discloses feeding 1,5-pentanediol to make PHA comprising of 5-hydroxyvalerate (limitation recited in claims 1 and 3) and feeding 1,4-butanediol to make PHA comprising of 4-hydroxybutyrate (limitation recited in claims 1 and 4). Skraly also discloses using a 1,3-propanediol oxidoreductase isolated from *K. pneumoniae* (page 8). And since "it was routine to identify enzymes having the appropriate specificity for the cheap substrates which would in turn yield the

required monomers" (bottom of p. 9 to top of p. 10 of the Brief) and diol oxidoreductases were well known in the art (BRENDA), it would have been obvious to one having ordinary skill in the art to either use a 1,3-propanediol oxidoreductase isolated from *K. pneumoniae* or substitute other well known diol oxidoreductases, such as those disclosed by BRENDA, to achieve the predictable result of converting diols into their required PHA monomers.

(3) According to MPEP 2143.01 the motivation to combine references can be found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." Therefore, disclosure of using diols other than 1,4-butanediol and 1,5-propanediol does not have to be explicitly taught by Skraly. Skraly discloses the desirability of producing PHA from non-traditional pathway, such as (1) producing PHA from monomers other than 3-hydroxybutyrate, which can improve flexibility and reduce crystalline of the resulting PHA polymer, such as 5-hydroxyvalerate and 4-hydroxybutyrate (page 6) and (2) new inexpensive starting materials for PHA synthesis, such as diols, 1,3-propanediol, 1,5-pentanediol, 1,4-butanediol and 1,2-propanediol, which are converted into their respective PHA monomers, 3-hydroxybutyrate, 5-hyroxyvalerate, 4-hydroxybutyrate and 2-hydroxypropionate (pages 1, 6 and page 8). Therefore, one having ordinary skill in the art would have been motivated to use other diols in order to make PHAs efficiently and incorporate monomers that can improve flexibility and/or reduce crystallinity of PHAs (page 1 of Skraly). Thus, one having ordinary skill in the art would have been motivated to modify the method of Skraly by using other diols.

At bottom of p. 11 of the Brief, appellant argues that Madison does not make up for the deficiencies in Skraly because Madison does not disclose any teaching that one could or should make PHA from monomers converted from diols.

Appellant's arguments are not found persuasive. The rejection is not based on Madison alone. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Madison is relied upon for providing evidence of the high level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. As applicants have stated, "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief filed June 5, 2006, pages 24-25). The combined teachings of the references of Skraly and BRENDA is relied upon for a method of producing PHAs using alternative pathways, wherein organisms are genetically engineered to covert cheap diol substrates into PHA monomers.

At middle of p. 12 of the Brief, appellant argues use of improper hindsight reasoning.

Appellant's argument is not found persuasive. In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, since (1) knowledge of making PHAs from cheap diol substrates using a recombinant *E. coli* expressing a diol oxidoreductase/aldehyde dehydrogenase was known (Skraly), (2) knowledge of genes that convert diols into their required monomers was known (Skraly and BRENDA), (3) knowledge of genes necessary in PHA synthesis and PHA synthesis in recombinant organism were well known (Madison), and (4) "it was routine to identify enzymes having the appropriate specificity for the cheap substrates which would in turn yield the required monomoers" (bottom of p. 9 to top of p. 10 of the Brief), a method of making PHA comprising of 5-hydroxyvalerate, 4-hydroxybutyrate or 2-hydroxypropionate converted from 1,5-pentanediol, 1,4-butanediol or 1,2-propanediol, respectively, or converting other structurally similar diols, such as 1,6-hexanediol into 6-hydroxyhexanoate and 1,2-ethanediol into 2-hydroxyethanoate by using *E. coli* expressing diol oxidoreductase available in the art was well within the level of one having ordinary skill in the art at the time the invention was made. Therefore, it would have been obvious to one having ordinary skill in the art to either use a 1,3-propanediol

oxidoreductase isolated from *K. pneumoniae* or substitute other well known diol oxidoreductases, such as those disclosed by BRENDA, to achieve the predictable result of converting diols into their required PHA monomers.

At bottom of p. 12 through bottom of p. 12 of the Brief, appellant argues that one having ordinary skill in the art would not have had a reasonable expectation of success because one cannot simply string several genes together and expect a complex metabolic pathway to work in a living organism since **(1)** Skraly acknowledges that the co-monomer PHB-CO-3HB is more difficult to produce because propionyl-CoA must be converted to 2-hydroxy-valeryl-CoA by a ketothilase, **(2)** the art fails to define the required pathway, and **(3)** one of skill in the art would engage in undue experimentation due to the large number of enzymes that could possibly be used and the large number of combinations of enzymes that are possible.

Appellant's arguments are not found persuasive.

(1) Co-monomer PHB-CO-3HB, which comprises 3-hydroxybutyrates, is not recited in the rejected claim(s).

(2) Skraly does disclose/define an alternative pathways for producing PHAs from cheap diol substrates, such as 1,2-propanediol (converted to 2-hydroxypropionate), 1,4-butanediol (converted to 4-hydroxybutyrate) and 1,5-pentanediol (converted to 5-hydroxyvalerate) (pages 1, 6-7 and 9) and a method of engineering an organism to produce PHAs from two different diols using a 1,3-propane diol oxidoreductase and an aldehyde dehydrogenase (see p.8).

(3) Undue experimentation is unrelated to whether one having ordinary skill in the art would have had a reasonable expectation of success. Nevertheless, one of skill in the art would not engage in undue experimentation because as Appellant has stated, "it was routine to identify enzymes having the appropriate specificity for the cheap substrates which would in turn yield the required monomers" (bottom of p. 9 to top of p. 10 of the Brief).

Further, BRENDA discloses several diol reductases that oxidize diols and that have been cloned and expressed in *E. coli,* including the *K. pneumoniae* diol oxidoreductase used by Skraly and in the instant invention. For example, BRENDA discloses a 1,3-propanediol dehydrogenase isolated from C. *freundii* which oxidizes several diols, 1,3-propanediol, 1,2-propanediol and 1,4-butanediol, and its expression in *E. coli* (pages 2-3). This enzyme has been cloned and expressed in *E. coli* (pages 10 and 12) as evidenced by Daniel et al. (J Bacteriol. 1995 Apr;177(8):2151-6 - form PTO-892). Daniel et al. also teaches that said enzyme oxidizes all primary, secondary and tertiary alcohols (Daniel et al. on page 5152). Even though 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol are not explicitly listed as one of the substrates, since the enzyme is able to oxidize primary alcohols and diols containing two primary alcohols, one having ordinary skill in the art would have reasonably expected the enzymes to oxidize 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol. Also, appellant pointed out in a previous Appeal Brief (filed June 5, 2006) that "all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and

integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (pages 24-25). Therefore, since enzymes that can convert different diols into their required PHA monomers were well known in the art, one of ordinary skill in the art would not have engaged in undue experimentation.

Further, MPEP 2143.02 makes clear that absolute predictability is not required, only some degree of predictability. In view of the teachings as described above, one of ordinary skill at the art at the time of the invention would have had at least some degree of predictability of making PHAs from cheap diol substrates using an *E. coli* (which endogenously produces an aldehyde dehydrogenase) genetically engineered with genes necessary for PHA synthesis and gene encoding a diol oxidoreductase taught by Brenda or Skraly since 1,3-propanediol dehydrogenase isolated from C. *freundii* and K. *pneumoniae* have a wide range of substrate specificity. Therefore, it would have been obvious to one having ordinary skill in the art to generate PHAs comprising of 5-hydroxyvalerate, 4-hydroxybutyrate or 2-hydroxypropionate from 1,5-pentanediol, 1,4-butanediol or 1,2-propanediol, respectively, or convert other structurally similar diols, such as 1,6-hexanediol into 6-hydroxyhexanoate and 1,2-ethanediol into 2-hydroxyethanoate by using *E. coli* expressing diol oxidoreductase available in the art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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